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| | C | US- | | | |
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Chemical and biochemical microreactors

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Research into the fundamental and practical advantages of using micrometre scale reactors for chemical and biochemical applications is now growing at a considerable rate. This review tracks such developments, illustrating their inherent strengths and identifying areas where further development of a technology is poised to revolutionise significant areas of synthetic chemistry and biochemistry. ©2000 Elsevier Science B.V. All rights reserved.

Keywords: Microreactor; Gas phase; Heterocyclic chemistry; Catalysis; Biochemistry

1. Introduction

In recent years research and development of miniaturised chemical systems has grown dramatically, allowing the realisation of the micro total analytical system (μ -TAS), which the reader will find well-documented [1–6] and described, elsewhere in this issue of TrAC. In a less dramatic way the application of similar technology to that used for μ -TAS has also led to the development of so-called micro-chemical reactors [7–9]. However, simply reducing the size of a chemical reactor because technology is available goes beyond just being gimmicky and this review will attempt to illustrate some of the intrinsic features such as the spatial and temporal control of reagents and reactants that can be achieved under the diffusion-limited and unique thermal properties that exist at the micrometre scale [10].

Areas that have attracted most research to date have centred on gas and liquid phase reactions covering heterogeneous and homogeneous catalysis, catalytic oxidation, heterocyclic synthesis, and photochemical reactions. In particular, the processes described have clearly indicated the value

of using microreactor technology for solution-based chemistry and bio-application in areas such as chemical discovery and development. In addition we should not underestimate the relevance microreactors will have as tools for purely research and teaching applications across a wide range of scientific disciplines.

Microreactors exhibit numerous practical advantages when compared with traditional batch-scale synthesis, not least is the demand for a high standard of safety, which includes the transportation and storage of toxic, explosive or otherwise harmful materials. In such cases microreactors offer the capability to carry out production on site at the point of demand. The removal of potentially significant large-scale plant accidents associated with thermal runaway could also be envisaged due to the inherent thermal dissipation possible in microreactor devices. Indeed it has been demonstrated that reactions can be performed beyond their current explosive limits by adopting microreactor technology [11]. The whole aspect of heat management, enabling mass and heat transfer to be extremely rapid, leads inevitably to a higher level of reaction control and reactant manipulation at any one point within a device. In addition, the problems associated with traditional scale-up could be overcome by reactor scale-out producing the required quantity of raw material. Adopting a scale-out philosophy coupled with large-scale microreactor fabrication technology, it is possible to see how the optimisation of reaction conditions on a single device could be extended, allowing multiple numbers of single units referred to as 'parallel scale-out'. By adopting such an approach, the reaction efficiency and throughput capacity allowing the production of material on a supply and demand basis could be achieved without the need to redesign or validate the reaction methodology. Thus one can conclude that microreactors applied to the field of chemical and biochemical synthesis offer greater reaction control and selectivity, which in turn can be optimised through a scale-out methodology creating a safe and efficient approach to chemical discovery and production.

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2. Microreactor fabrication and applications

Currently, microreactor devices are produced using a number of techniques, for example wet etching [12], injection moulding [13] and laser microforming [14] using a variety of materials, such as noble metals, polymers, ceramics, glass and silica. Noble metal devices are suitable for fast exothermic heterogeneously catalysed reactions and this has been successfully demonstrated for the partial oxidation of methane to syngas using a honeycomb, structured rhodium catalyst device [15]. Metal devices are commonly generated using microlamination techniques in which thin laminates of metal are stacked forming channels and partitions. The channels generated are achieved by pressure stamping or using photochemical machining techniques. Mobilisation of organic solutions in metal devices requires the use of micro-pressure pumping systems that can lead to an increase in internal pressure which may or may not be seen as an advantage for a number of reactions.

Glass and silica devices are suitable for a variety of applications allowing, for example, fast reaction screening for drug discovery applications and heterogeneously catalysed reactions. At the University of Hull, drug discovery screening applications are being developed in glass microreactors using model systems such as the Wittig synthesis based on aldehyde functionality [16]. In addition, heterogeneous catalytic reactions based around a modified Suzuki reaction have been investigated as these offer spatial and temporal delivery of reactants to the catalytic surface and in situ base generation to be exploited [17]. This type of device exhibits chemical inertness and temperature stability and can also mobilise aqueous and organic solution via electroosmotic flow (EOF) which has numerous advantages including minimal back pressure, no mechanically moving parts and therefore a corresponding high reliability with minimal hydrodynamic dispersion. In addition, the opportunity to exploit electrokinetic separation in conjunction with EOF offers considerable scope to temporally and spatially control of reaction intermediates and products [10].

3. World-wide development

This special issue of TrAC serves well to demonstrate that the whole area of microtechnology applied to chemical processes is a rapidly expanding area of research and there are now a number of growing research groups around the world focusing on chemical microreactor applications. Jensen's group from the Department of Chemical Engineering at the Massachusetts Institute of Technology has a particular interest in the safety aspects of reactions, especially the explosive and toxicity issues relating to the production of a variety of compounds at the point of demand. This has been demonstrated with the production of a microreactor for organic peroxides generated from acid chlorides [11]. In addition, advances in thin film metal membranes have allowed the development of a hydrogen flux device that has additional application for hydrogenation reactions [18]. With a similar emphasis on safety, Ehrfeld's group at the Institut für Mikrotechnik, Germany, has been a prime mover in developing microreactors for the reduction of exposure to hazardous materials. Recently a microreactor has been developed for the Andrusow reaction allowing the synthesis of the toxic material hydrogen cyanide [15] to be achieved. Success in controlling a high temperature reaction will now allow systems for a variety of similar high temperature reactions to be developed. Other work has centred on the direct fluorination of aromatic compounds in which greater product sensitivity was achieved [15].

The research group of Wegeng and Drost at the Pacific Northwest National Laboratories in Richland, WA, has generated a variety of applications for the development of an automotive fuel processor and heat pumps, microengineered devices for hydrogen-rich fuel streams and the development of microchannel contractors for gas absorption and microdevices for solvent extraction [15].

Other related applications include the fabrication of a multistep synthesis device by Orchid Biocomputers, USA, which will enable the synthesis of over 100 compounds to be performed simultaneously, the development by Bergveld of a microdialysis device and counterflow heat exchanger at the University of Twente, Netherlands [15] and developments in Sweden in the area of biocatalysis [19]. In addition, Yager's group from Washington State have extensively described the development and

fabrication of T-shaped manifolds for chemical reactions and sensors [20]. Karube's group has described the development of an enzyme-immobilised column with electrochemical flow cell for glucose detection using micromachining techniques [21]. In the UK, the Chemical Engineering Department at the University of Sheffield has been investigating the use of stacked gas-phase microchannels. The work, led by Ray Allen, has extensively modelled the fundamental parameters that affect the scaling of reactions [22] based on channel hydraulic diameter, reaction intensity and reactor proportions.

Finally, Haswell's group at the University of Hull has been working for a number of years on various areas of microreactor research, focusing in particular on establishing the practical capabilities of microreactor devices using already established synthetic chemistry reactions including the Suzuki catalytic-based reaction [17], and the characterisation of fluidic control demonstrated using the Wittig synthesis [16]. The group has a number of on-going projects looking at multi-stage synthesis and experimental design methods based on microreactor technology.

4. Research themes

In this section a selected number of examples have been chosen from the literature to illustrate the novelty microreactors can bring to the area of synthetic and bio-applications. The review is in no way meant to be definitive or wide ranging but will serve to illustrate some of the current developments that are occurring in a rapidly developing field.

Chambers et al. [23] have reported the development of a microreactor in which elemental fluorine has been used to allow both the selective fluorination and perfluorination of organic compounds in a simple controllable manner. The synthesis of fluorine-containing organic compounds has many inherent safety issues such as safe handling and temperature control. Chambers outlined the potential benefits of the microreactor used as being (i) a small inventory of fluorine in the reaction zone, (ii) an opportunity for good mixing and temperature control and (iii) simple reaction scale-up. Taking into account these criteria, Chambers designed the reactor outlined in Fig. 1. The microreactor is fabricated from a block of nickel in which a groove is machined (ca 500 μm) and sealed using a block of

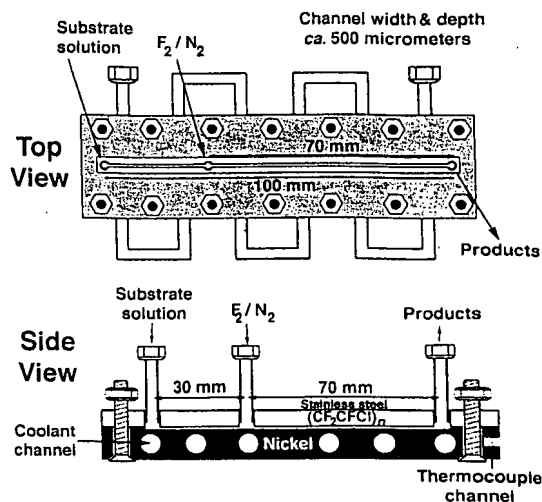


Fig. 1. Microreactor top and side view for elemental fluorine reactions.

polychlorotrifluoroethane. Liquid reactant and solvent delivery was achieved using pressure syringe pumps, whilst the fluorine in nitrogen was delivered from a small cylinder via a mass flow controller. Liquid-gas mixing was achieved using cylindrical flow and the products were trapped in polychlorotrifluoroethylene tubing and cooled. Residual gas was scrubbed using soda lime. The microreactor was shown to achieve the successful synthesis of a variety of selective fluorinations yielding 75% conversion derivatised from di(*m*-nitrophenyl)disulphide and for *p*-nitro systems 44% conversion was achieved using acetonitrile, 10% F_2 in N_2 (10 ml/min) at room temperature. Fluorination of β -dicarbonyl illustrated the catalytic effect by the fluorinated metal surface, giving a highly efficient conversion (step 5 to 6, 99%, step 7 to 8, 90% conversion) even though the overall yield was low (62%). The flow system obviously promotes the formation of the enol, which can be a limiting factor in large-scale reactors. Chambers also demonstrated that the microreactor could be used for perfluorination, which has many inherent safety issues. The overall product yield was 70% (stage 9 to 10, 52% conversion, yielding 91% and stage 11 to 12, 82% recovery, yielding 70%). The results obtained indicate a potential for elemental fluorine reactions to be achieved in the laboratory as well as on an industrial scale.

The group of Jensen et al. [18] has reported the development of a novel palladium membrane to allow for a controlled selective hydrogen flux.

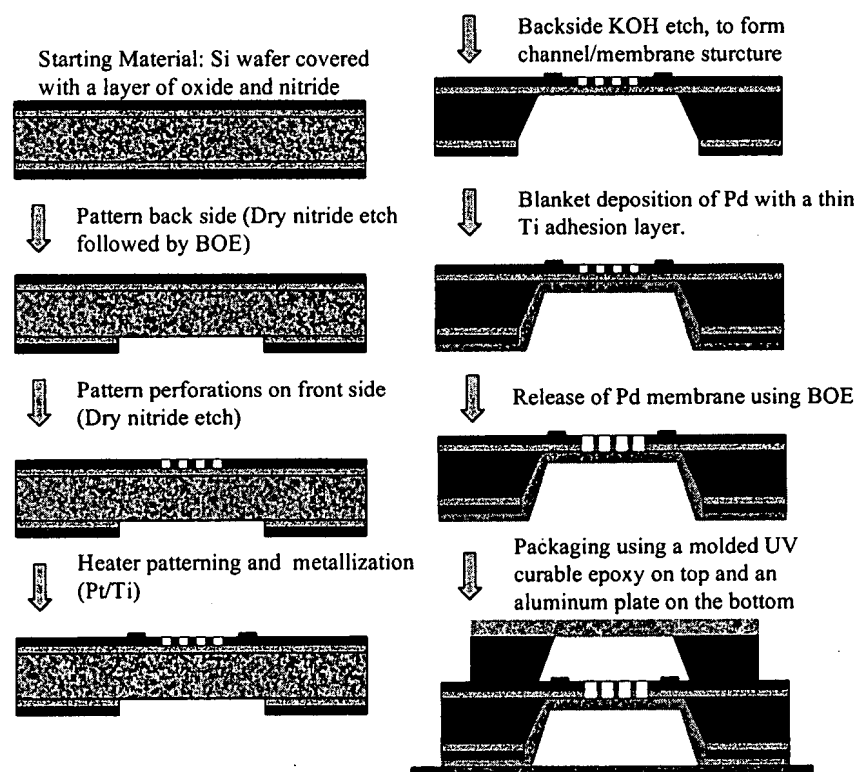


Fig. 2. Palladium membrane fabrication process.

The membrane was specifically designed for incorporation with microelectromechanical systems, microfluidic devices allowing hydrogen separation in palladium micromembranes resulting in two separate streams being generated. In addition the potential to perform hydrogen purification applications such as hydrogenation and dehydrogenation are possible with this form of a membrane reactor. Fig. 2 outlines the type of device fabrication used. The device is a two-channel flow system separated by a thin membrane layer that is fabricated from composite layers of perforated silicon nitride, silicon oxide that supports and insulates the palladium metal from the integrated temperature sensing and heater elements. The overall channel geometry is 1.2 cm long and slightly less than 700 μm wide. The extensive device fabrication method allows the use of arbitrarily thick or thin palladium films, due to the support being porous and so offering attractive cheaper metal alternatives. An intrinsic property of the device is the symmetric heater design, allowing a large area of the membrane to be heated whilst maximising the area in the centre for perforations and hydrogen flux. The micromembrane perme-

ability and selectivity were characterised as a function of the hydrogen pressure gradient and average membrane temperature. A mixture of hydrogen and nitrogen (1:9) together with pure hydrogen was fed into the device. At elevated temperatures, the membrane generated a notable exit drop in hydrogen concentration and increased nitrogen, indicating the presence of a selective hydrogen flux. In addition, a membrane separation factor of over 1800 was determined. At an average temperature of 500°C, a hydrogen flow rate of 0.5 sccm was observed for a single active heater segment, at a pressure of 0.1 atm, corresponding to a flux of 600 sccm/ cm^2 . These results indicated that the micro-fabricated membranes are potentially much more efficient than large-scale devices. Finally, the membrane's potential for hydrogenation and dehydrogenation was investigated using a hydrogen/nitrogen mixture exposed to air in the device. The hydrogen permeating through the membrane reacted with oxygen to form water, which condensed on the cold top of the surface.

At the Third International Conference on Micro-reaction Technology in Frankfurt am Main, Ger-

many, Worz et al. discussed the development of a high temperature hydrogen cyanide synthesis device using the synthetic Andrussow route [15]. The device was fabricated enabling the investigation of the influence of isothermal processing and extremely rapid cooling of a hot, reactive product gas and a highly exothermic reaction with extreme handling and exposure risks. The reaction was achieved in a 60 μm diameter microchannel, which allowed the reactant gas to be heated to 1000°C within 1 ms. The microreactor feasibility was compared with published results achieved in ceramic and metal monoliths with channel geometries of 0.5–1 mm. With the microreactor an increase in yield for hydrogen cyanide of up to 30% was obtained compared to standard methodology. The higher yields were attributed to the improved mass transfer because of the significant reduction in channel dimensions by at least one order of magnitude. In addition, the microreactor generated less than 2% ammonia and methane by-products compared to 59% ammonia and 27% methane in conventional reactors. The microreactor device demonstrated selective, high throughput conversion based on the Andrussow reaction, indicating that the device could easily be adapted allowing the development of a variety of high temperature reactions.

At the University of Hull, two solvent-based synthetic processes have been investigated as model systems to evaluate the potential of microreactors for such applications. The selected processes were heterogeneous catalysis based on a modified Suzuki synthesis [17] and homogeneous reactions based on Wittig chemistry [16]. The first example allowed an evaluation to be made of a flow injection-based methodology using the Suzuki reaction. The microreactor used was fabricated in borosilicate glass with channel geometries of 300 μm wide and 115 μm deep (Fig. 3). Reagent solutions

were mobilised via EOF assisted by the incorporation of a microporous silica structure [24], which was also used to immobilise the palladium as a heterogeneous catalyst bed. The synthesis of 4-cyanobiphenyl was achieved at room temperature, via in situ generation of base giving a product yield of $67 \pm 7\%$ ($n=6$). Conventional laboratory batch methodology using the same reaction criteria as used with the microreactor was performed, however the reaction was reflux for 8 h under an inert atmosphere, giving a non-optimised product of 10%. Further work is currently proceeding to improve the product yield in the microreactor by developing a post-reaction separation system, which allows the recycling of starting material and the isolation of a pure product.

The second reaction is based on Wittig chemistry [16] in which 2-nitrobenzyltriphenylphosphonium bromide and a variety of aldehydes, for example methyl-4-formylbenzoate in dry methanol and sodium methoxide, were reacted in a T-shaped manifold (300 μm wide and 100 μm deep). The microreactor is currently being evaluated for its potential to perform diverse generic chemistry for a variety of syntheses as this clearly has value in reaction optimisation and combinatorial applications. The reaction was optimised using EOF assisted by the incorporation of microporous silica frits, generating a product yield for 2:1 reaction stoichiometry of 70% (10% increase compared with traditional synthesis). This was achieved using continuous flow of both reagents through the microreactor for 20 min. Further reaction optimisation using a series of injections performed over a 20 min period gave a yield of 59% (1:1 stoichiometry, 11% increase over traditional batch synthesis). The optimised reaction was also investigated for a further four aldehydes, demonstrating the general applicability of the method. Fig. 4 shows a series of image captures using an optical microscope at which the coloured reaction intermediate (ylide) can be seen. In plate 1, the reagents are being moved by EOF from both the left- and right-hand side and a clear interface can be seen. Poor flow control however is observed due to the formation of the intermediate in the left-hand channel, which was readily corrected by the slight increase in the voltage applied to the left-hand electrode (plate 2). This allowed the reactants to move down the central channel due to the increase in flow of the reagent from the left-hand channel. As the reagents are pumped by EOF turning the power off sees the

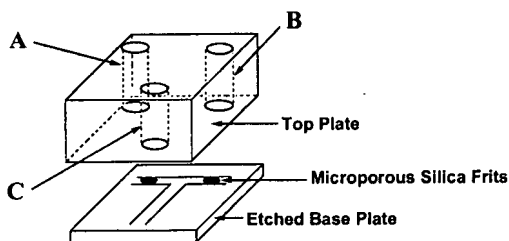


Fig. 3. Schematic diagram of the T-shaped manifold used in the reactor for the Suzuki coupling.

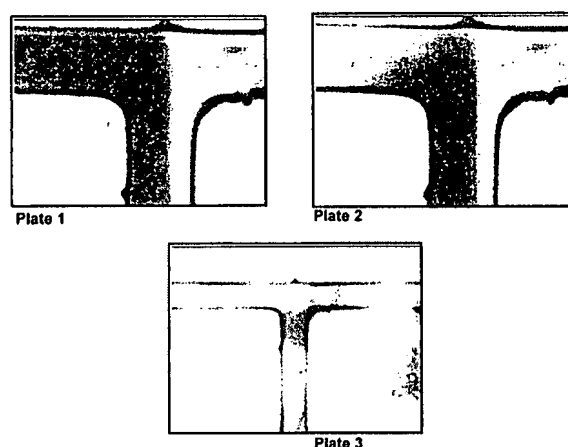


Fig. 4. A series of images captured using an optical microscope in which the coloured reaction intermediate (ylide) flow profile can be observed.

loss of colour rapidly (plate 3) thus demonstrating that the spatial position of a reaction can be controlled with relative ease. As indicated, the resulting optimised methodology is currently being developed for combinatorial screening implying increased analysis speed but also demonstrating diversity for a variety of reagents.

In the field of bio-catalysis, Laurell et al. [19] have investigated the use of porous silicon as a carrier matrix in microstructured enzyme reactors, increasing the surface area onto which enzymes could be coupled. The microreactor was fabricated using a flow-through cell comprising 32 channels, 50 μm wide, spaced 50 μm apart and 250 μm deep in silicon, p-type (20–70 $\Omega\text{ cm}$) generated by anisotropic wet etching. The porous matrix was generated by anodisation in hydrofluoric acid and ethanol, producing three different pore morphologies at 10, 50 and 100 mA/cm^2 current densities. Glucose oxidase was immobilised onto the three porous microreactors and onto the non-porous reference device. The enzyme activity was monitored using a colorimetric assay. The devices were used to study glucose turnover rates, which were deemed to be good and illustrated the potential value of using porous silicon as a support in enzyme reactors. Using the microreactor fabricated at 50 mA/cm^2 , they found that the enzyme activity was increased 100-fold compared with the reference reactor. The microreactor was also coupled with an FIA system allowing glucose monitoring. The system gave a linear response up to a 15 mM concentration of glucose.

Laurell et al. [25] further investigated the use of porous silicon by varying the matrix depth in micro enzyme reactors. Using p-type (20–70 $\Omega\text{ cm}$) orientated silicon, in which porous silicon was generated on a planar surface and on an isotropically pre-etched high aspect ratio parallel channel reactor, different silicon morphologies were generated for each sample type by varying the anodisation time, and two current densities. Standard methodology was used to immobilise the glucose oxidase on to the silicon surface, and the enzyme activity was monitored by colorimetric assay. In comparison to the identical non-porous material the results obtained for the silica matrices indicated a 170-fold increase in catalytic turnover for a reactor pore depth of 10 μm . Above this level, catalytic activity levelled out. The results clearly indicate the variation in catalytic activity with the difference in matrix depth for both the planar and reactor structures. In addition, work reported by Laurell [26] has demonstrated an increase in enzyme activity of up to 350 times, using the porous silicon as an enzyme carrier matrix.

5. Concluding remarks

From the examples given above we are already seeing evidence that microreactors can bring novelty and real practical advantages to reaction-based chemistry. The advantages come essentially from the thermal, spatial and temporal control possible in such devices, coupled with the capability to monitor reactions *in situ* while operating if necessary under controlled temperature, pressure and atmospheric conditions. In simple terms, microreactors reduce many of the practical difficulties associated with performing chemical reactions based on traditional methods. Indeed many of the experimental observations reported to date could not have been possible using conventional methodology. Work is currently under way by the authors and other leading research groups that will rapidly push the technology towards working devices for combinatorial and controlled multi-stage syntheses. In this context we should not forget the inherent advantage the technology offers in terms of being able to rapidly perform a reaction and screen for products with minimal practical intervention and reagent consumption. Issues over product volumes will always be raised when using microreactors but given the inherent practical advantages of the methodology,

these will no doubt already be attracting the necessary engineering and design developments to realise appropriate system scale-out. However many question the time it will take for this emerging technology to reach the market place. To this end one should not underestimate the role of the vendor organisations who will no doubt respond to reduce many of the cultural and practical difficulties associated with the technology due to the tremendous commercial potential that will catalyse this area of scientific research over the next few years.

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